UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SAB-EHC-88-013

OFFICE OF
THE ADMINISTRATOR

Hon. Lee M. Thomas
Administrator
U.S. Environmental Protection
Agency
401 M Street SW
Washington, D.C. 20460

Dear Mr. Thomas:

On August 13-14 1987 the Halogenated Organics Subcommittee of the Science Advisory Board's Environmental Health Committee met in Washington, D.C. to review two documents prepared by EPA's Office of Research and Development that assess health effects associated with dichloromethane (methylene chloride). These documents included:

- a June 1987 Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments, and
- a July 1987 Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology.

The Subcommittee's evaluation of these documents is presented in two parts: 1) a discussion of scientific issues related to pharmacokinetics and metabolism, and 2) review of specific issues pertinent to the addendum. The Subcommittee focused less attention on the former document because much of its scientific content overlapped with the Addendum.

The Subcommittee concludes that the Addendum was one of the best documents it has reviewed in terms of its clarity, coverage of the data and analysis of scientific issues. This document clearly demonstrates the potential utility of pharmacokinetic data in risk assessment. EPA should continue to use this approach in future risk assessments, whenever scientifically possible.

For reasons discussed in the attached report, the Subcommittee concludes that the level of uncertainty is greater and the hazard posed by dichloromethane may be less than that expressed by the categories of EPA's cancer risk assessment guidelines.

The Subcommittee appreciates the opportunity to conduct this scientific review. In behalf of the Subcommittee we request that the Agency formally respond to the scientific advice provided in its attached report.

Sincerely,

Norton Nelson, Chair
Executive Committee

Richard A. Griesemer, Chair
Environmental Health Committee

John Doull, Chair
Halogenated Organics Subcommittee

Halogenated Organics Subcommittee
Review of the June 1987 Draft Technical Analysis of New Methods and Data Regarding Dichloromethane Hazard Assessments: and July 1987 Draft Addendum to the Health Assessment Document for Dichloromethane: Pharmacokinetics, Mechanism of Action and Epidemiology

Pharmacokinetics and Metabolism

The application of a physiologically based pharmacokinetics (PBPK) model presented in the document is generally well conceptualized and organized. This application represents a novel approach that can sharpen EPA's ability to refine human risk estimates in the future. The Subcommittee commends EPA for incorporating such information into the weight of evidence determination of the carcinogenic potential of dichloromethane. Adoption of the Reitz-Anderson model, with certain modifications, is a positive step forward for the Agency's risk assessment process. The critical analysis of the constraints of the model are thoroughly discussed and scientifically balanced. EPA, for example, is justified in adjusting the estimates of Reitz-Anderson for breathing rates traditionally used in EPA models. The rationale for using surface area factor adjustment, and contrary arguments, are clearly described.

The PBPK model has appeared in the published peer reviewed literature. The novel applications of the latest data concerning the model that were presented at the meeting are new and received enthusiastic support from the Subcommittee, which also recommends publication of this approach. The Subcommittee recognizes that validation will be required for this and other compounds before using this approach generally for human risk calculations.

One possible problem is that the metabolic conversion of dichloromethane by different animal species by either the cytochrome P-450 oxidase system (mixed function oxidase or MFO) or the glutathione-S-transferase system (GST) was not supported by data indicating that measurements in each species were conducted at conditions optimal for pH, ionic strength or temperature for that substrate in that tissue for each specific species. Unless such conditions are utilized, interspecies quantitative data may be meaningless, and the basis for the use of this approach in human risk estimation could be flawed.

Comparative in vitro studies with rat, mouse, hamster and human cytosol showed that the dichloromethane-GST conjugation rates in humans were at least 50 times lower than in mice. The Subcommittee points out that: 1) mice have the highest activity and liver tumor induction that correlates with GSH-metabolite production above saturation of the MFO system; 2) hamsters have much lower activity and no liver tumors; and 3) humans have even lower activity indicating very low, if any, liver tumor inducing potential for dichloromethane. There was a good correlation between the relative rates of dichloromethane-GSH conjugation and susceptibility of liver tumors. The conclusion that, at low exposure levels, the carcinogenic hazard to humans

from dichloromethane appears very low needs to be clearly stated in the document.

The document could be simplified by eliminating the Chapter 7 discussion of a "rationale" for surface area scaling and replacing it with the statement on page 107 that, "The fact that there is no clear basis for choosing the use of surface area correction or not...is a weakness of the current state-of-the-art of quantitative risk assessment."

Discussion of Specific Scientific Issues Related to the Addendum

1. In considering an overall weight of evidence approach to risk assessment, other factors, such as the nature of the animal tumor response, mechanistic data (such as binding of the chemical to DNA), genotoxic activity and epidemiological data should also be discussed.

2. In evaluating the tumor data, the Subcommittee urges caution in extrapolating the existing animal bioassay to humans. Although dichloromethane induced both lung and liver tumors in the mouse models, these observations occurred only at high doses which likely influenced the compound's overall metabolism. Other bioassays in other species, or at lower doses in mice, induced negative results. The fact that the Reitz-Anderson model is able to predict these responses suggests that an interspecies correction factor based on surface area may not be necessary for extrapolating the tumor data to humans. This is particularly true when hamster and rat data (GSH transferase) are considered using the PBPK analysis. The observation of benign mammary tumors and salivary gland tumors in rats should not be used as strong evidence for human carcinogenic potential given the uncertain significance of these lesions. The benign mammary tumors have very low potential for predicting malignancy even in the rat, and salivary gland tumors were reported in only one of the studies.

3. EPA should discuss the findings of several investigators (Shumann et. al., Dow Chemical; Green et. al., ICI, U.K.) that indicate that dichloromethane or its metabolites do not exhibit any potential to alkylate liver or lung DNA following in vivo exposure. Such findings raise the clear possibility that dichloromethane may have produced its carcinogenic responses in mice by non-genotoxic mechanisms, and may include an important contribution of cytotoxicity in the overall tumorigenic process. Such data became particularly relevant as carcinogenicity was observed only at extremely high exposures and was absent at lower, potentially noncytotoxic doses.

4. Critical uncertainties remain regarding the relationship between dose to target tissues and tumor incidence, since little information on the mechanism of action is available for dichloromethane. The Subcommittee accepts EPA's use of a surface area scaling factor for delivered dose as appropriate for calculating an upper bound estimate, but it views this usage as more conservative than the usual "default" assumption from the Agency cancer guidelines, scaling administered dose by surface area from animals to humans. Further research may indicate that, at least for some substances, scaling delivered dose on the basis of body weight is more appropriate than scaling by surface area.

5. The degree of nonlinearity in the dose reponse relationship for delivered dose is an important source of uncertainty. As noted on page 110 of the Addendum, EPA uses the linearized multi-stage model to calculate an upper bound estimate. The true dose response curve may fall off more rapidly than a linear relationship at low doses. Biological information supporting a non-linear or threshold type of dose response relationship is potentially important for risk management decision making because it becomes less likely that the default plausible upper bound linear estimate will be an accurate estimate of human risk, especially at low exposure levels in the ambient environment.

6. The Subcommittee was presented with a brief report on the current status of the Kodak epidemiological study of dichloromethane. A slight excess of pancreatic cancer deaths has been separately reported. However, the study is based only on death certificate data and has not included a histopathologic review of biopsies or surgical specimens from such patients. The incidence of pancreatic cancers tended to cluster, and only with further surveillance of the population can a more definitive statement be made on human health risk. The clinical diagnosis of pancreatic cancer is difficult and may be easily confused with other abdominal malignancies. Thus, without pathologic confirmation, the Subcommittee cannot necessarily conclude that an excess of pancreatic cancer deaths has occurred. However, neither can it be concluded that dichloromethane is safe for humans at the occupational exposure levels seen in the study. The Agency should determine the criteria of the Kodak epidemiological study necessary to substituting the animal derived risk estimate with a human derived risk estimate. Finally, the Subcommittee recommends the continuation of this important study.

7. Although there is an impressive weight of evidence implicating metabolites of dichloromethane in tumors, the possibility should not be discounted that the actual tumor inducing agent is the parent compound(s). In order to present a more balanced document, this possibility should be discussed at greater length, perhaps in Chapter 8.

8. Both the scaling factor and the shape of the dose response relationship are important areas for further work in order to aid development of risk assessment methods that incorporate available scientific data and judgement on biological mechanisms. As better information is developed on pharmacokinetics, pharmacodynamics and mechanisms for chemical carcinogenesis, it should be possible to further reduce uncertainties in human risk estimates.

9. For all of the above reasons, therefore, the Subcommittee concludes that the level of uncertainty is greater and that the hazard for dichloromethane may be less than that expressed by the Agency's classification system in its cancer risk assessment guidelines.

More detailed discussion of these and other issues by individual Subcommittee members has been forwarded to the Office of Research and Development.

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
Halogenated Organics Subcommittee
Roster for August 13-14, 1987 Review of the Draft
Assessment Documents for Dichloromethane

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